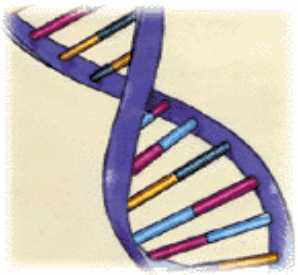
A publication of the Indiana State Department Of Health Genomics Program

TRANSCRIPTIONS:

Genetics and Genomics in Public Health



Autumn, 2006

Volume 1

Issue 5

Inside this issue:

Syndrome of the season:

Marfan Syndrome

A basic review by Susan Romie & Karen Barnett

A matter of debate among medical historians is whether Abraham Lincoln had Marfan syndrome, an inherited connective tissue disorder. Lincoln's famously gaunt appearance is far from definitive proof, but he did have certain physical traits commonly associated with Marfan syndrome. These include an extremely tall, slender build, a narrow face, loose joints, and spinal or chest wall abnormalities.

Marfan syndrome is an inherited disorder of the connective tissue. It is estimated that one person in every 3,000-5,000 has Marfan syndrome, or about 50,000 people in the United States. Marfan syndrome is one of the more common autosomal dominant inheritable disorders.

Marfan syndrome affects three major organ systems of the body: the heart and circulatory system, the bones and muscles, and the eyes. The genetic mutation responsible for Marfan was discovered in 1991. It affects the body's production of fibrillin, which is a protein that is an important part of connective tissue. Because the patient's fibrillin is abnormal, his or her connective tissues are looser than usual, which weakens or damages the support structures of the entire body.

Marfan syndrome is caused by a single gene for fibrillin on chromosome 15, which is inherited in most cases from an affected parent. Between 15 and 25% of cases result from spontaneous mutations. Mutations of the fibrillin gene (FBNI) are unique to each family affected by Marfan, which makes rapid genetic diagnosis impossible, given present technology.

Be Aware of the Signs of Marfan Syndrome

- Tall, thin stature
- Disproportionately long arms and legs
- Scoliosis
- Protruding or indented chest
- Flat feet
- Lens dislocation
- Nearsightedness
- Mitral valve prolapse
- Aortic dilatation

The diagnosis of Marfan syndrome is made by taking a family history and a thorough examination of the patient's eyes, heart and bone structure. The examination should include an echocardiogram, a slit-lamp eye examination and a work-up of the patient's spinal column. Diagnosis can remain uncertain due to the mildness of symptoms and the lack of a family history.

If a diagnosis is made, lifestyle changes may be necessary.

Cytomegalovirus Infection in Pregnancy

Christin Griffis, MS, Jessica Claybrook, MS, and David D. Weaver, M.D.

Cytomegalovirus

Cytomegalovirus (CMV) is a herpes virus that is spread through contact with saliva, blood, urine, feces, tears, breast milk, semen, and cervical and vaginal secretions (1). By the age of 40, 50-85% of Americans have been infected with CMV (2), many unaware of such infection. This is the case since in 90% of healthy children and adults, CMV infection is asymptomatic (3). If symptoms do occur, they can include mononucleosis-like symptoms, such as malaise, sore throat, cough, fever, chills, nausea, and muscle pain. Other potential symptoms include hepatosplenomegaly, lymphadenopathy, infertility, and recurrent spontaneous abortion (4).

Like herpes simplex virus, once an individual is infected with CMV, the virus remains in the body throughout life. The virus is normally dormant, but reactivation can occur and may be asymptomatic or result in the above symptoms. During recurrent infections (reactivation), individuals are able to spread the virus (2). Rarely, individuals may become infected with a different strain of CMV, as there is more than one strain known to infect humans (5).

Maternal Infection and Transmission

In addition to the above symptoms, pregnant women may experience oligohydramnios or polyhydramnios and placental thickening (4). Maternal infection is spread to the fetus or infant through three routes: via the placenta, bodily fluids during birth, or through breast milk or maternal secretions postnatally (4).

Fetal Infection

During pregnancy, the virus can cross the placenta and infect the fetus directly (4), and can occur during a maternal primary infection or maternal virus reactivation. Maternal primary infection occurs in 0.7-6% of pregnancies worldwide and poses the greatest risk to the fetus (4). With primary infection, the average transmission rate to the fetus is 40% (1), but only 10-20% of infected fetuses will be symptomatic at birth (5, 6). Infection with a second strain of CMV would result in similar risks (6). Maternal virus reactivation occurs in 1-14% of pregnancies (1). The average transmission rate is 0.15-2%, with symptomatic infection occurring in 1% of infants at birth (1, 5). Gestational age at the time of maternal exposure does not affect transmission rates to the fetus, but CMV disease in the infant appears to be more severe with infection before 20 weeks gestation (1). CMV does not affect organogenesis; it does, however, damage organs that already are formed (5).

Neonatal Infection

Twenty-five to fifty percent of infants exposed to infected maternal vaginal secretions (primary or reactivation) during birth become infected with CMV (4). However, according to the Centers for Disease Control and Prevention (CDC), the majority of infants exposed during birth are asymptomatic so the risk of neonatal transmission does not warrant delivery via cesarean section (2). The risk of symptomatic infection, however, is increased for premature infants (6).

Postnatal Infection

It is estimated that 40-60% of infants breastfed by infected mothers (primary infection or reactivation) for more than one month become infected (2). According to the CDC, very few infected infants are symptomatic and the benefits of breastfeeding outweigh the risk of infection (2). The risk for symptomatic infection is increased for premature infants (6).

Congenital Infection

Congenital CMV infection, symptomatic and asymptomatic, has occurred in approximately 1% of all live births in developed countries; however, only a small number of these cases have severe disease as a result (4, 5, 6, 8). In general, symptoms are more severe in infants infected after a primary maternal infection than those infected after maternal viral reactivation (5, 8). Infants with symptomatic infection can present with intrauterine growth retardation, hydrocephalus, agenesis of the corpus collosum, microcephaly, thrombocytopenia, anemia, petechiae, hydrops, chorioretinitis, hepatosplenomegaly, and hepatitis with jaundice, and stillbirth (4). The most common long-term sequelae in symptomatic infants are mental retardation (70%); sensorineural hearing loss (50%), which can be progressive; dental defects (30-40%); and vision deficits (20%) (4). Infants with symptomatic congenital CMV have a 10-30% mortality rate, with 10% occurring in the newborn period. The most common causes of newborn deaths are related to liver failure, bleeding disorders, and bacterial infection (3, 4, 7).

Continued on page 3

Cytomegalovirus Infection in Pregnancy, cont.

Five to fifteen percent of infants who have had prenatal CMV infection but are asymptomatic during infancy will develop abnormalities in early childhood including sensorineural hearing loss, which may be progressive and bilateral; learning disabilities or mental retardation; seizures; chorioretinitis; and defects of tooth enamel (4,5, 7). CMV is considered the most common infectious cause of mental retardation, learning disabilities, and deafness in children (4, 5).

Screening and Diagnosis

Despite the incidence of CMV, the CDC does not recommend routine laboratory screening for all pregnant women, as this would be quite costly (2). Furthermore, if a maternal infection were detected, there is no way to determine if the fetus will become infected or how severe symptoms may be (5). In addition, there is no fetal treatment available during pregnancy (5). However, the CDC does recommend that the need for screening be determined on a case-by-case basis, for instance in women with mononucleosis-like symptoms during pregnancy (2). To make a diagnosis of congenital CMV infection, virus isolation from bodily secretions must be performed in the first two weeks following birth. Isolation after that point in time could reflect perinatal or postnatal infection (4, 5).

Treatment and Prevention

Treatment of symptomatic adults with ganciclovir has shown a reduction in symptoms; however, treatment in pregnant women is not offered because this drug crosses the placenta and may be carcinogenic and teratogenic (4). Neonatal treatment with ganciclovir in clinical trials has been shown to reduce symptoms (4).

To prevent infection during pregnancy, women are encouraged to wash their hands with soap and water after contact with bodily fluids, especially after changing diapers (1). Women should refrain from mouth-to-mouth kissing with children attending daycare and should not share food, drinks, or utensils during pregnancy. Women who are in non-monogamous relationships should use condoms during intercourse (1).treatment in pregnant women is not offered because this drug crosses the placenta and may be carcinogenic and teratogenic (4). Neonatal treatment with ganciclovir in clinical trials has been shown to reduce symptoms (4).

This overview was provided by the Indiana Teratogen Information Service (INTIS), which offers free information to questions regarding the risk of medication, infection, or other exposures during pregnancy and lactation to pregnant women or health care providers. To reach INTIS with additional inquiries, please contact (317) 274-1071. INTIS is funded in part by a MCH Title V grant.

References:

1) Cytomegalovirus and pregnancy. (2001) www.OTISpregnancy.org
2) Cytomegalovirus (CMV) infection. (2005) www.cdc.gov/ncidod/diseases/cmv.htm
3) Gaytant MA, Steegers EAP, Semmekrot BA, Merkus HMMW, and Galama JMD. (2002) Congenital cytomegalovirus infection: review of the epidemiology and outcome. *Obstetrical and Gynecological Survey* 57:245-256
4) Damato EG, Winnen C. (2001) Cytomegalovirus infection: perinatal implications. *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 31:86-92
5) Daniel Y, Gull I, Peyser MR, Lessing JB. (1995) Congenital cytomegalovirus infection. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 63:7-16.
6) REPROTOX on-line database, Micromedex® Healthcare Series, 2006.
7) TERIS, Teratogen Information Service on-line database, Micromedex® Healthcare Series, 2006.
8) Gayant MA, Rours GI, Steegers EAP, Galama JMD, Semmekrot BA. (2003) Congenital cytomegalovirus infection after recurrent infection: case reports and review of the literature. European Journal of Pediatrics 162: 248-253

CMV FACTS

1. Between 50% and 80% of adults in the United States are infected with CMV by 40 years of age.
2. CMV is the most common virus transmitted to a pregnant woman's unborn child.
3. Approximately 1 in 150 children is born with congenital CMV infection
4. Approximately 1 in 750 children is born with or develops permanent disabilities due to CMV.
5. There is no available vaccine for preventing congenital CMV disease. The Institute of Medicine has ranked the development of a CMV vaccine as a highest priority.

Feb. 6, 2006 National Center for Infectious Diseases

Autism Spectrum Disorder

Edited by Karen Barnett

Autism is the most common condition of autism spectrum disorders (ASD), also known as pervasive developmental disorders. This group of developmental disorders includes Asperger's syndrome, Rett's syndrome, childhood disintegrative disorder and pervasive childhood developmental disorder not otherwise specified. Three distinctive behaviors characterize autism: difficulties with social interaction, verbal and nonverbal communication problems, and repetitive behaviors or obsessive traits.

Autism is usually apparent and diagnosed by age 3, and in some cases, as early as 18 months. The Indiana Birth Defects and Problems Registry (IBDPR) accepts diagnosis for ASD up until age five. Autism affects approximately one to two per 1,000 people and is about four times more common in males than in females. However, females with the disorder present more severe symptoms and greater cognitive impairment. The number of children with a diagnosis of autism has been rising continuously for over a decade, but the extent to which diagnostic changes and improvements in ascertainment contribute to this increase is unclear.

Scientists are not sure what causes autism, but they do believe that genetics and the environment both play a role. Most researchers are absolutely convinced that the cause is biological rather than psychological. There is still controversy over neurological differences in the brains of autistic people and the rest of the population. However, it does appear from evidence obtained through autopsies, MRI and PET scans, that there are subtle cellular changes in the autistic brain. The increased incidence of seizures (20-30% develop seizures in adolescence) also points to neurological differences.

Some specific theories as to the cause of autistic symptoms:

- food allergies
- genetic causes
- viral causes
- vaccines (including Thimersol, which was phased out by the FDA in 2001)
- immunological ties
- structural cerebellar changes
- brain injury

There is no standard, universally accepted treatment for autism, in fact, every single method has its detractors. General approaches may be summarized as follows:

- biochemical (medication, food and vitamin supplementation)
- neurosensory (sensorial integration, auditory training, facilitated communication)
- psycho-dynamic (holding therapy, psychotherapy and psychoanalysis, option institute)
- behavioral (behavior modification with and without aversives, TEACCH)

ASDs are complex disorders and may involve other neurological or genetic problems. Therefore a comprehensive evaluation should entail neurologic and genetic assessment, along with in-depth cognitive and language testing. In addition, measures developed specifically for diagnosing autism are often used. These include the Autism Diagnosis Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS-G). Still another instrument often used by professionals is the Childhood Autism Rating Scale (CARS). Customarily, an expert diagnostic team has the responsibility of thoroughly evaluating the child, assessing the child's unique strengths and weaknesses, and determining a final diagnosis.

For every child eligible for special programs, each state, including Indiana, guarantees special education and related services. The Individuals with Disabilities Education Act (IDEA) is a Federally mandated program that assures a free and appropriate public psychologist, social worker, school nurse, or aide.

There are national organizations such as the Autism Society of America (ASA), as well as state and local ASA chapters. The Indiana Resource Center for Autism has selected state resources for information, training, advocacy & empowerment for persons with disabilities. http://www.iidc.indiana.edu/irca/

Expanded Services for Adults with Genetic Conditions

The Department of Medical and Molecular Genetics at the Indiana University School of Medicine has recently expanded its services for adult patients with genetic conditions. The Adult Genetics Clinic provides clinical evaluations, diagnostic testing, coordination of care, and genetic counseling for adults with a known or suspected genetic condition. Services are also available for family members of affected individuals who are interested in an evaluation and risk assessment. The clinic is overseen and staffed by Adeel Zaidi, M.D. & Jessica Claybrook, M.S. Patients can be scheduled by calling (317) 274-8660 or (800) 486-6124. Questions regard the clinic and services provided should be directed to Jessica Claybrook, M.S. at (317) 278-8847.

2006 Immunization Plan

The CDC announced that the 2006 Childhood and Adolescent Immunization Schedule has been released, with the updated schedule including new recommendations that will help protect adolescents from meningitis and pertussis, and all children from hepatitis A. The 2006 immunization schedule is published in CDC's *Morbidity and Mortality Weekly Report*, available at www.cdc.gov.mmwr

The new tetanus, diphtheria and acellular pertussis recommendation stems from the availability of new Tdap booster vaccines intended to reduce the number of whooping cough cases among adolescents. The recently licensed meningococcal conjugate vaccine also is being recommended. Under the updated schedule, these vaccines would be routinely administered to children when they are 11 to 12 years of age. The updates also include hepatitis A vaccination to include all children at 1 year of age; hepatitis B vaccination for all infants at birth; and influenza vaccination to now include children at least 6 months of age.

Autism Risks

Pregnancy factors, parental psychiatric history and preterm delivery may be associated with the risk of autism, according to a 2005 study supported in part by the CDC. Some of the specific factors the study found to be associated with the risk of autism included breech presentation at birth, delivery before 35 weeks, a parent who had a diagnosis of schizophrenia-like-psychosis before the date that autism was diagnosed in the child, and low birth weight at delivery.

CME credits available! Take a look at what AAFP has to offer on autism and other subjects.
http://www.aafp.org/acfgenomics.xml

Will EHRs Help Spread Germs?

Drug-resistant bacteria can survive as long as 24 hours on computer keyboards, a study revealed, highlighting what could be a growing threat as hospitals increase investment in technology for electronic health records (EHRs) and other computer-based tools.

The study, carried out at Northwestern Memorial Hospital in Chicago, found that keyboards can contaminate the fingers—bare or gloved– of a health professional, who could then transfer bacteria to the patients, Reuters reported.

Indiana State Department of Health

2 North Meridian Street, 8C-01
Indianapolis, IN 46204

Judith A. Monroe, M.D.
State Health Commissioner

Sue Uhl
Deputy State Health Commissioner

Karen Barnett, M.S., M.A.T.,
Editor

Bob Bowman, M.S., Genomics &
Newborn Screening Programs
Director

Maternal & Child Health Services
Indiana State Department of Health

Visit Us on the web:
http://www.in.gov/isdh/programs/genomics/

Continued from page 1

Marfan Syndrome

Physical activities - Because Marfan syndrome appears in many forms, recommendations about exercise vary widely. For example, people with dilation of the aorta may be asked to avoid the usual team sports.

Isometric exercises (such as weight lifting or rowing) and contact sports in which a blow to the chest could occur (such as football or hockey) also may be off-limits. Many people with the Marfan syndrome can participate in modified physical and recreational activities. A cardiologist can give advice about this.

The Indiana University Marfan Syndrome Program was recently established with the following mission:

- Provide excellence in patient care to individuals and families with Marfan syndrome.
- Facilitate Marfan syndrome research through a patient registry.

Enhance professional and public knowledge of Marfan syndrome through educational programs.
The Kathryn L. Ober Marfan Syndrome Clinics are the only clinics in Indiana dedicated to Marfan Syndrome and staffed by board certified medical geneticists. The Adult Marfan Syndrome Clinic, located at Indiana University Hospital in Indianapolis, is staffed by medical geneticist and internist, Dr. Adeel Zaidi, and genetic counselor, Jessica Claybrook. Appointments for this clinic may be made by calling 317-278-6650, or toll free, 1-800-486-6124.

The Pediatric Marfan Syndrome—Medical Genetics Clinic, located at Riley Hospital in Indianapolis, is staffed by medical geneticists, Drs. David Weaver and Wilfredo Torres, and several experienced genetic counselors. Appointments may be scheduled by calling 317-274-1057.

For more information on Marfan syndrome and local support services, contact Susan Romie, coordinator for the Indiana University Marfan Syndrome Program: 317-278-6650, or toll free at 1-877-MARFANS, or e-mail at sromie@iupui.edu.